REMARKS/ARGUMENTS

Claims 1-31 are pending. Claims 1, 4-6, and 9 are presently under examination and stand rejected. Reconsideration of the claims is respectfully requested.

In the Advisory Action dated November 20, 2003, the Office maintained the rejection of claims 1, 4 to 6 and 9 under 35 U.S.C. §103(a) as allegedly obvious over Rabinovitch, Diabetes, 43:613-621 (1994) [Rabinovitch] and Lenschow et al., Immunity, 5:285-293 (1996) [Lenschow '96; IDS-Y], in view of either King et al., Eur. J. Immunol., 25:587-595 (1995) [King; IDS-W] or Webb et al., Blood, 86:3479-3486 (1995) [Webb; IDS-AQ].

It is respectfully submitted that the state of the technological field at the priority date of the instant application was in contradiction to the findings of the inventors disclosed in this application. In particular, the picture for the artisan was (1) that CD28 antagonists (not agonists as recited in the presently pending claims) can be efficacious in treatment of autoimmune diabetes and other autoimmune conditions, and (2) that antigen-specific tolerance is involved in the prevention of autoimmune diabetes.

(1) CD28 Antagonists

Applicant has previously drawn the Office's attention to relevant references available to the public shortly prior to and at the priority date of the instant invention. These references emphasize the use of agents that antagonize CD28 signaling in the prevention of autoimmune conditions, including but not limited to autoimmune diabetes.

Autoimmune conditions demonstrated to be suitably treated by CD28 antagonist therapy include transplant graft rejection (Lenschow et al, Science, 257:789-792 (1992) using CTLA-4Ig administration), lupus erythematosus (Finck et al., Science, 265:1225-1227 (1994) using CTLA-4Ig administration), allogenic pancreatic islet transplantation (Levisetti et al. J. Immunol, 159:5187-5191 (1997)) and autoimmune diabetes (Lenschow et al. J. Exp Med. 181:1145-1155 (1995) using either CTLA-4Ig or anti-B7-2 mAb). Hence, these references, at the priority date, focused greatly on antagonism of CD28 function in the prevention of autoimmunity, and suggested a broad spectrum utility of CD28 antagonists in such related immune-mediated disease conditions.

Contrastingly, the cited references fail to teach that an agonist of the CD28 receptor could be efficacious for the treatment or prevention of autoimmune disease. The instant application was the first teaching which demonstrated that a CD28 agonist is effective in treating autoimmune diabetes. In the absence of the teachings of this application, therefore, an artisan with ordinary skill would be convinced that CD28 antagonism would be the only useful method of preventing autoimmune disease.

The cited references directly contradict the findings disclosed in the instant application and further confirms that a skilled artisan at the time of the invention would not have been motivated to expect that a CD28 agonist would be efficacious in treating autoimmune diabetes. The Applicant further submits, and has provided evidence in support, in the form of the Affidavit of Dr. Terry Delovitch filed on July 25, 2003, particularly paragraphs 6 to 12, that such an artisan would not have a reasonable expectation of success in preventing autoimmune diabetes with CD28 agonist therapy, or would even consider such experimentation as "worth a try".

The Office's position, that the combination of cited §103 references (Rabinovitch, Lenschow, King and Webb) suggests that CD28 agonists would effectively treat autoimmune diabetes, requires deliberate disregard for the contradictory suggestions contained in these references, and the inferences which can be drawn therefrom, as well as the Declaration of Terry Delovitch. The Office's position is in contrast to the requirements of MPEP 2143.01, where it is required that conflicting information must be weighed by the Office to understand the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference may discredit another. The quantity of conflicting data previously discussed, regarding the utility of CD28 antagonists in autoimmunity and the timing of the CD28 signaling blockade, would not lead one of skill in the art to the conclusions drawn by the Office.

The Office's position relies on the presumption that Lenschow et al. (1996) (report that CD28-/- knockout mice developed elevated incidence of autoimmune diabetes) would lead one of skill in the art to expect that a completely opposite approach (CD28 agonist therapy) would lead to decreased diabetes. Neither this publication, nor any other cited

reference, indicates that this would be a reasonable assumption. Furthermore, such an expectation by an artisan would be in direct conflict with the evidence indicated in Lenschow (1996) at page 285, right column, that CTLA-4Ig-based antagonism of CD28 function yields prevention of autoimmune diabetes in mice. There is therefore no foundation in this reference for the combination asserted by the Office.

(2) Antigen-Specific Tolerance

The references cited by the Office further demonstrates that the state of the technological field at the priority date emphasized antigen-mediated tolerance as a method of preventing autoimmune diabetes. In particular, this is illustrated by the Office's citation of Rabinovitch et al. as relevant to this application. Although the Applicant contends that this reference is irrelevant, it is noted that Rabinovitch advocates the use of (1) microbial adjuvants as therapy for autoimmune diabetes onset and (2) administration of autoantigens (namely GAD65) as a method of tolerizing against the pancreatic antigen attacked by autoimmunity during autoimmune diabetes. The former approach had been discredited in references prior to the priority date, as has been demonstrated by the Applicant in previous submissions, yet the Office contends that the administration of specific autoantigens is relevant in the rejection.

It is respectfully submitted that the Office has misapplied the contents of Rabinovitch. In contrast to the non-antigen specific CD28 agonist treatment disclosed in this application, Rabinovitch reported that administration of specific autoantigens *in vivo* is useful in abating the onset of autoimmune diabetes. As was well known to the artisan prior to the priority date, such antigen-specific immune tolerance is not mediated by the induction of anergy, or T cell hyporesponsiveness, as has been well characterized in the context of autoimmune diabetes (Kaufmann et al. Nature. 366:69-72 (1993)). Unlike the upregulation of cytokines demonstrated by the present inventors, Rabinovitch teaches away from the use of T cell anergy against Th1 cytotoxic functions involved in the progression of autoimmunity. The method described in Rabinovitch does not have any relevance to CD28 agonist stimulation and hence would not have indicated to one skilled in the art that the claimed method would have had a reasonable expectation of success.

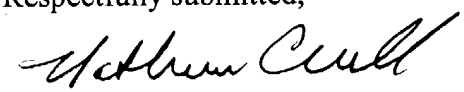
As noted in MPEP 2142, obviousness requires at least (1) some suggestion or motivation in the cited references to combine the references or teachings available to an ordinary artisan, and (2) a reasonable expectation of success. No such suggestion or demonstration was available in the cited references that agonists of CD28 are efficacious in autoimmune diabetes therapy. The Office, armed with the teachings of the instant application, is using impermissible hindsight to find obviousness.

In conclusion, the §103 references cited by the Examiner (Rabinovitch, Lenschow, King and Webb), whether viewed singly or in combination, do not provide a reasonable expectation of success regarding the utility of CD28 agonist stimulation in treating or preventing diabetes. In fact, the findings of the present invention are completely opposite to the state of the technological field as at the priority date. A skilled artisan would not have been motivated to consider the approach used in this application as fruitful in light of the knowledge previously available in the field.

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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